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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/526,173	03/02/2005	Caroline J Springer	620-358	6894
23117	7590	08/21/2006	EXAMINER	
NIXON & VANDERHYE, PC 901 NORTH GLEBE ROAD, 11TH FLOOR ARLINGTON, VA 22203			NAGUBANDI, LALITHA	
			ART UNIT	PAPER NUMBER
			1621	

DATE MAILED: 08/21/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	10/526,173	SPRINGER ET AL.	
	<b>Examiner</b>	<b>Art Unit</b>	
	Lalitha Nagubandi	1621	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 23 June 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 123-164 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 123-154 and 160-164 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)                        | 4) <input type="checkbox"/> Interview Summary (PTO-413)                     |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)               | Paper No(s)/Mail Date. _____  |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date <u>03/02/06</u>  | 6) <input type="checkbox"/> Other: _____                                    |

***Detailed Office Action***

***Status of the Claims***

Claims 123-164 are pending in this application.

***Election/Restriction***

Applicant's election of Group I (claims 123-164) and the species recited in claim 161 **formula (P-1)**, in the reply filed on June 23<sup>rd</sup> 2006, is acknowledged. Claims 155 –159 are withdrawn from consideration as not being directed to the elected species.

***Response to Argument***

Applicants' remarks in response to the previous office action dated May 23<sup>rd</sup>, 2006 regarding restriction requirement has been noted. The word 'anticipated' has been inadvertently made hence it has been withdrawn. However, the cited reference teach compounds which are structurally similar to those of the instant application rendering obviousness. Further, the inventions listed as groups I, II and III do not relate to a single general inventive concept. Hence, the election requirement is made FINAL.

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***Specification***

The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicants' cooperation is requested in correcting any errors of which applicant may become aware of in the specification.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

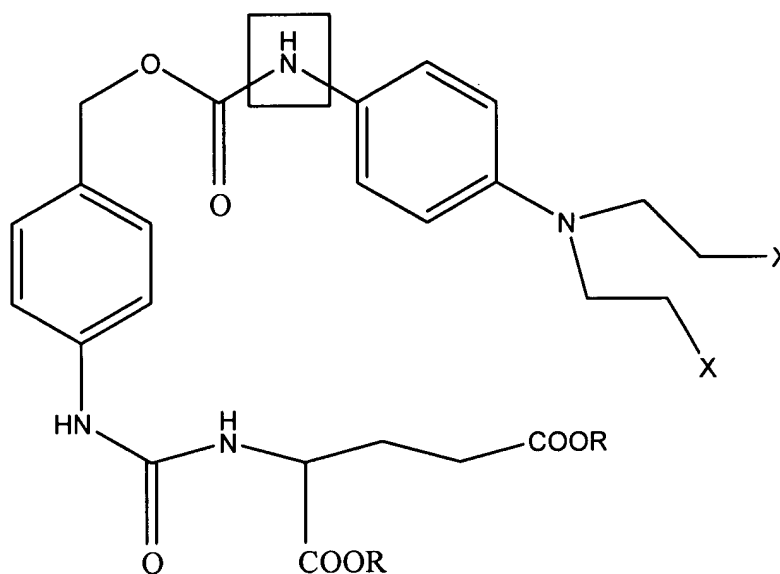
Claims 123-154 and 160-164 are rejected under 35 U.S.C. 103(a) as being unpatentable over Springer et al (WO 96/22277, 25 July 1996 and US Pat. No. 6,005,002).

Applicants claim N-substituted Nitrogen Mustard Prodrugs of formula (P-1).

### Determination of Scope and content of the Prior Art (MPEP§2141.01)

Springer et al teach (see: Fig. 3, compounds 19 and 20, WO 96/22277, 25 July 1996)

nitrogen mustard prodrugs with novel lipophilic protecting groups, and processes for their production.



### Ascertainment of the difference between the Prior Art and Claims (MPEP §2141.02)

The difference between the instant compounds and Springer et al is that the instant compounds require N-substitution of the carbamoyl N (indicated within the box), which is between the benzyl group and the phenyl group as shown above. Springer et al is silent on protecting the NH group and does not disclose any method for N-protection in WO 96/22277, 25 July 1996.

**Finding of prima facie obviousness – rational and motivation (MPEP § 142-2143)**

It is sufficient if a reference compound is so closely related to claimed compound that a chemist would find the difference an obvious variation; thus, claims are refused where the difference is primarily the one, which exists between a secondary and a tertiary amine. *Ex Parte Bluestone*, 135 USPQ 199 (1961).

Applicants recite in the specification (see page 9, lines 5-10), that they have “discovered unexpectedly, corresponding compounds, in which the nitrogen atom is substituted, for example, with a C<sub>1-7</sub> alkyl group, offer one or more pharmacological advantages, including but not limited to: (a) improved activity; (b) improved selectivity (e.g., against tumour cells versus normal cells); (c) reduction in required dosage amounts; (d) reduction in required frequency of administration; (e) reduced intensity of undesired side-effects; (f) fewer undesired side effects”.

Based on the above teachings, when a person of ordinary skill in the art examines the data provided by the applicants (Please see: Specification, page nos. 81, 82 Cytotoxicity Data :**Table 1** and **Table 2**), it is not clear to conclude that N-Me or N-substituted compounds has improved activity over unsubstituted compounds. For example, if the results of **CP-2** (IC<sub>50</sub> is 179.8 ; Degree of activation (fold) 101.6 ) **P-1**(IC<sub>50</sub> is 184.7 ; Degree of activation (fold) 124.0) , are compared and **CP-2** shows a degree of activation of 101.6 at IC<sub>50</sub> 179.8 and **P-2** shows degree of activation of 124.0 at IC<sub>50</sub> 184.7. Is it because the compounds exhibit higher degree of activation at higher concentrations, if it is not so then for the record, the data provided does not adequately teach the superiority of the invention over the prior art.

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Therefore the subject matter as a whole would have been obvious to one of ordinary skill in the art and one would have been motivated to modify the compounds cited above at the time of invention, and the ordinary artisan would have had a reasonable expectation of success and hence it is a prima facie obvious.

### ***Conclusion***

No claims are allowed

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lalitha Nagubandi whose telephone number is 571 272 7996. The examiner can normally be reached on 6.30am to 3.30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K. Page can be reached on 571 272 0602. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Lalitha Nagubandi  
Patent Examiner  
Technology Center 1600

August 16<sup>th</sup>, 2006.



Samuel A Barts Ph.D.

Primary Patent Examiner  
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